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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/469,492	06/06/95	WEINER H	10107/16959-0

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DARBY & DARBY
805 THIRD AVE
NEW YORK NY 10022

EXAMINER	
FRICKRIL,B	
ART UNIT	**PAPER NUMBER**
1817	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 08/469,492	Applicant(s) Weiner et al.
	Examiner Benet Prickril	Group Art Unit 1817

☒ Responsive to communication(s) filed on *Jun 6, 1995* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *37-58* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *37-58* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This application is a continuation of application Serial No. 07/843752 filed 2/28/92. Claims 37-58 are pending. Claims 1-36 have been canceled.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). A computer readable form (CRF) of the sequence listing was submitted. However, the CRF could not be processed by the Scientific and Technical Information Center (STIC) for the reason(s) set forth on the attached CRF Diskette Problem Report.

Applicant is required to comply with the sequence rules, 37 CFR 1.821 - 1.825 within the time period allotted for response to this Office action. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for response beyond the SIX MONTH statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached CRF Diskette Problem Report with the response.

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

Parent applications 07/460852 and 07/596936 do not contain as a part of their disclosures any mention of glucagon or gamma amino decarboxylase, which are essential features of the instant application. Therefor the application is assigned an effective filing date of 2/28/92 which is the filing date of parent application 07/843,752.

3. Claims 37-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The generic claims are directed to a method and pharmaceutical dosage form for treating an autoimmune disease using a bystander antigen, while more limited embodiments are claimed which comprise the bystander antigens gamma amino decarboxylase and glucagon. The specification provides support for gamma amino decarboxylase only by way of its inclusion in the list of bystander antigens in Table 1 on page 19. No other reference to or guidance concerning gamma amino decarboxylase is present in the specification as filed, and therefore the artisan could not determine how to obtain the antigen or what appropriate dosages should be administered absent undue experimentation. Moreover, the term gamma amino decarboxylase is not recognized in the art as defining a discrete enzyme species, and does not appear to be an enzyme which has been assigned an EC (Enzyme Commission) number as for other enzymes known in the art. With respect to the bystander antigen glucagon, the specification provides support only by way of its inclusion in the list of bystander antigens in Table 1 and a statement

(page 19 line 15 ff.) that glucagon is not an autoantigen. No other reference to or guidance concerning the antigenic properties of glucagon is present in the specification as filed, and therefore the artisan could not determine what appropriate dosages should be administered absent undue experimentation. Although glucagon is well known, it is not recognized in the art as a therapeutically useful bystander antigen. Applicants have not provided any guidance to allow the artisan to determine what diseases are treatable by their methods, which are generic to any autoimmune disease, what dosages are therapeutically useful, what level of purity is necessary, or what length of time the administration should continue. Without at least rudimentary guidance to address these factors the artisan could not carry out the invention absent undue experimentation.

Applicants use of the term "non-immunologically" in claims 37 and 48 finds no direct support in the specification, wherein there is no teaching that the administered materials are not effective to treat a disease non-immunologically. The specification is silent concerning the non-immunological activity of various antigens while offering lengthy discussions of possible immunological mechanisms of action. Since no specific references to "non-immunological" treatments incorporating the antigens of the invention are provided, and it is uncertain what the genesis of the term is (mechanism of action?, clinical observations/sequelae?) the artisan could not determine its intended meaning. Furthermore, in view of the complex etiology of autoimmune diseases, particularly with respect to the predictability of the therapeutic effect of various potential autoantigens or bystander antigens, the artisan could not determine what antigens might be useful, how to purify these antigens or what level of purity is necessary for therapeutic success, or a host of other parameters related to the preparation and administration of

potential antigens, or what disease or diseases would be treatable with a given bystander antigen without considerable and undue experimentation. Applicant's claims appear to merely invite further experimentation in order to determine just what constitutes a useful antigen for oral or nasal administration for the purpose of treating some undefined autoimmune disease without providing the requisite guidance necessary to allow the artisan to determine what these antigens are.

4. Claims 37-58 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "is not effective to treat said autoimmune disease non-immunologically" in claims 37 and 48 is unclear. It is uncertain what "non-immunologically" refers to. Is this term meant to suggest the mechanism of action of the administered material, is some particular type of activity implied, or is some other meaning intended. It is unclear what limitations are intended in defining the term "non-immunological" for autoimmune conditions in which the mechanism of action is ambiguous or, as for diabetes, in which both "immunological" and "non-immunological" modes of action find experimental support.

Claims 45 and 55 are unclear as to what is meant by a "substantial" or "substantially" with respect to a decrease in the blood sugar level. How large is "substantial"? Is said decrease to be compared with some standard blood sugar level? For example, is there a lower limit to the percentage change in blood sugar level above which "substantial" applies? Moreover, is the

autoimmune condition to be treated limited to type 1 diabetes mellitus, or is some other condition pertaining to changes in blood sugar level -and presumably requiring some undefined bystander antigen, also being implied?

Claims 49-58 recite the limitation "inhalable dosage form" in reference to parent claim 48. There is no antecedent basis for this limitation in claim 48, which is drawn to a pharmaceutical dosage form.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 48-50 and 52-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Merck [Merck Manual, Fifteenth Ed., Ch. 94 pages 1087-1088, Merck & Co., Rahway, NJ (1987)] .

Merck teaches a pharmaceutical or inhalable dosage form of the bystander antigen glucagon in a pharmaceutically acceptable carrier. The dosage form of Merck inherently possesses all of the properties recited in applicant's claims when administered by the routes recited by applicant, including the ability to elicit suppressor T cells in order to stimulate release of TGF-β.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 37, 38, 40-45, 48, 49, 51-55, and 58 are rejected under 35 U.S.C. 103(a) over Foster [Harrison's Principles of Internal Medicine, 9th Edition] in view of Davydov et al. [U.S. Patent 4,529,589] or Ecanow [U.S. Patent 4,963,526].

Foster teaches the treatment of type 1 diabetes mellitus by administering insulin to humans, but does not teach oral administration. Davydov et al. disclose an oral form of insulin in a pharmaceutically acceptable diluent for use in treating diabetes mellitus. Ecanow teaches an oral dosage form of insulin for treating diabetes. It would have been obvious to administer the oral dosage form of insulin as taught by Davydov et al. or Ecanow for the treatment of diabetes as taught by Foster because the oral forms of insulin as disclosed by Davydov et al. and Ecanow have the advantage of eliminating the need for using injection as a mode of administering insulin. The formulations of Ecanow and Davydov et al. appear to meet any limitation of "non-immunological" as disclosed by applicants, particularly in light of the uncertainties of the definitions of "non-immunologically" and "substantial decrease" as previously discussed. Taken as a whole, Foster, Ecanow and Davydov provide ample motivation such that one skilled in the art would administer an autoantigen such as insulin for treatment of diabetes.

10. Claims 48-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merck [Merck Manual, Fifteenth Ed., Ch. 94 pages 1087-1088, Merck & Co., Rahway, NJ (1987)] in view of Harvey [Ch. 36 in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA (1980). see pages 669-671].

Merck teaches a pharmaceutical or inhalable dosage form of the bystander antigen glucagon in a pharmaceutically acceptable carrier. The dosage form of Merck inherently possesses the properties recited in applicant's claim when administered by nasal, mouth, or inhalation routes, including the ability to elicit suppressor T cells in order to stimulate release of

TGF-β. One skilled in the art would recognize that a bystander antigen, whether autoantigenic or nonautoantigenic, would possess immunosuppressive epitopes which may or may not be recognized by immune system cells contributing to a given disease condition, and that a portion of the bystander antigen containing said immunosuppressive epitope would be effective in carrying out the invention. Therefore it would have been obvious to one skilled in the art at the time the invention was made to obtain fragments of a bystander antigen containing an immunosuppressive epitope or, in the case of an autoantigen, fragments of the bystander antigen containing an immunosuppressive epitope but not containing an epitope implicated in autoimmune disease causation, for the purpose of obtaining the inhalable dosage form as claimed by applicant. Motivation to obtain the appropriate fragment of the bystander antigen is provided by the knowledge in the art that pharmaceutically active regions of biomolecules, such as the bystander antigens of the instant invention, are capable of eliciting biological activity similar or identical to that of the parent biomolecule. Harvey is cited because it teaches the conventionality in the art of administering pharmaceutical dosage forms of substances by various routes of administration, including the oral route, for treatment of various conditions.

11. Claims 37-58 of this application conflict with claims of Application No.s 08/461591, 08/461662, 08/468996, 08/472016 and 08/472017. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either

cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

12. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 37-39, 41-45, 48, 49, and 51-55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,399,347. Although the conflicting claims are not identical, they are not patentably distinct

from each other because both sets of claims recite the same positive method steps and bystander antigens that are either identical to or obvious over those of the instant invention. Claims 1-7 of U.S. Patent No. 5,399,347 are directed toward treatment of arthritis using type II collagen, while the instant claims are generic to methods of treating autoimmune diseases and encompasses treatment of arthritis with collagen. U.S. Patent No. 5,399,347 also encompasses pharmaceutical or inhalable dosage forms of the bystander or autoantigen.

14. Claims 37, 38, 40, 42-45, 48, 49, and 51-55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 13, 14, 17, 19 and 20 of copending application serial No. 08/419502. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite the same positive method steps. Claims 1, 2, 4, 13, 14, 17, 19 and 20 of copending application serial No. 08/419502 are drawn to a method comprising administering myelin basic protein to a human by inhalation for treating multiple sclerosis and an inhalable dosage form of myelin basic protein. Both an inhalable dosage form and the autoantigen myelin basic protein are recited in the method of treatment.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 37-58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-10, 12, and 15-17 of

copending Application No. 08/328562. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending Application No. 08/328562 are directed to treatment of multiple sclerosis or arthritis with autoantigens, and are therefor encompassed within the broad genus of the instant claims. Application No. 08/328562 further discloses inhalable dosage forms of the autoantigens.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 37-58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 9, 11, 12, 13 and 15 of copending Application No. 08/279,275. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite positive method steps. Although the instant claims are broader in scope than those of copending Application No. 08/279,275, the genus of the instant claims covers the species of collagen autoantigens taught by the prior application. Application No. 08/279,275 also teaches pharmaceutical or inhalable dosage forms of the autoantigens.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 37-58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-19, 21, 24, and 27-39 of

copending Application No. 08/472016. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are generic to a wide range of bystander antigens and autoantigens which encompass the insulin autoantigen species of copending Application No. 08/472016. Both sets of claims are drawn to treatment of autoimmune conditions, and both recite pharmaceutical or inhalable dosage forms.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 37-58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 15-19, and 37-49 of copending Application No. 08/472017. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are generic to a wide range of bystander antigens and autoantigens for treatment of autoimmune conditions. Both sets of claims are drawn to treatment of autoimmune conditions, and both recite oral dosage forms.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Claims 37-45, 47-55, and 57 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37-41 of copending Application No. 08/461591. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are generic to a wide range

of bystander antigens and autoantigens for treatment of autoimmune conditions which includes the bystander antigen gamma amino decarboxylase. Both sets of claims are drawn to treatment of autoimmune conditions, and both recite oral dosage forms.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 37-58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 59-80 of copending Application No. 08/461662. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are generic to a wide range of bystander antigens and autoantigens for treatment of autoimmune conditions which includes the bystander antigens glucagon and gamma amino decarboxylase. Both sets of claims are drawn to treatment of autoimmune conditions, and both recite oral dosage forms.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claims 37-46 and 48-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37-41 of copending Application No. 08/468996. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are generic to a wide range of bystander antigens and autoantigens for treatment of autoimmune conditions which includes the

bystander antigen glucagon. Both sets of claims are drawn to treatment of autoimmune conditions, and both recite oral dosage forms.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. No claims are allowed.

General information regarding further correspondence

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1817.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benet Prickril, Ph.D., whose telephone number is (703) 305-5933. The examiner normally can be reached Monday through Thursday between 7:30 AM and 5:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, Ph.D., can be reached at (703)308-4310. The fax phone number for Art Unit 1817 is (703) 305-7939.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER
GROUP 1800

Benet Prickril, Ph.D.
December 27, 1996